

This is the post print version of the article, which has been published in Muscle and Nerve.
2018, 57 (6), 1014-1017. <http://doi.org/10.1002/mus.26050>.

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Pain in *SCN4A* mutated p.A1156T muscle sodium channelopathy - a postal survey

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Acknowledgments: This study was supported by the Finnish Association for the Study of Pain.

Number of words in abstract: 148

Number of words in manuscript (excluding abstract): 1438

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Running title: Pain in *SCN4A* mutation p.A1156T

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

None of the authors has any conflict of interest to disclose.

Pain in *SCN4A* mutated p.A1156T muscle sodium channelopathy - a postal survey

Abstract

Introduction: The p.A1156T mutation alters the function of the voltage gated sodium channel Nav1.4 on the muscle sarcolemma, causing a channelopathy without overt myotonia or periodic paralysis but with myalgic pain.

Methods: A postal survey was conducted to assess the prevalence and characteristics of pain and related symptoms in persons with the p.A1156T mutation. A specific questionnaire, intensity and interference subscales of the Brief Pain Inventory, pain drawing, Widespread Pain Index, quality of life (RAND-36), and the Beck Depression Inventory were completed.

Results: Twenty of 24 patients replied. Current pain was reported by 16 responders; the other 4 had experienced pain previously. Most commonly, pain was widespread and exercise-induced. The severity and the impact of pain on daily life were considerable although variable.

Discussion: This sodium channelopathy is another entity in the growing number of diseases causing widespread myalgic pain that resembles the pain seen in fibromyalgia syndrome.

Keywords: pain, myalgia, channelopathy, *SCN4A*, p.A1156T, postal survey

Introduction

Mutations of the skeletal muscle sodium (*SCN4A*) and chloride (*CLCN1*) channels can lead to non-dystrophic myotonias and other rare myotonic disorders.¹ More than 40 different mutations, typically dominant missense, of *SCN4A* have been characterized to date². Identical *SCN4A* mutations, however, can be observed in patients with different clinical phenotypes, indicating considerable heterogeneity in the genotype-phenotype correlations.²⁻⁴ A nucleotide change c.3466G>A in exon 19 of the *SCN4A* causes the amino acid change p.A1156T in domain III of the alpha subunit of the voltage-gated sodium channel Nav1.4.^{5,6} The alpha subunit, coded by the gene *SCN4A* located at the chromosome 17q23-25, facilitates ion transport through the cell membrane.

The p.A1156T mutation has been described in one Finnish family and two South-Korean patients who shared features of hyperkalemic periodic paralysis and paramyotonia congenita.^{5,6} We recently reported a series of 30 new patients with this mutation, and described the clinical consequences of this mutation. These patients presented with widespread pain, muscular stiffness and exercise and cold-induced cramps, but without signs of clinical myotonia, paramyotonia or periodic paralyses.⁷ According to the ExAC database, the frequency of the p.A1156T mutation in the Finnish population is 60/100 000, meaning that there are more than 3000 mutation carriers and (due to the adult onset of symptoms) approximately 1000 affected individuals in Finland.⁷

Muscular pain is a frequent symptom in non-dystrophic myotonias, as reported by approximately 80 % of the patients.^{8,9} The severity of symptoms of *SCN4A* related myotonias can vary from very mild ones producing minimal or no interference with daily life to ones that have a severe impact.⁹

The aim of this postal survey was to assess the prevalence, characteristics, and severity of pain, muscular, and depressive symptoms and quality of life, in patients with the p.A1156T mutation-associated sodium channelopathy.

Materials and Methods

A postal survey was conducted in spring 2016. The study was approved by the local ethics committee and all participants gave written informed consent. The reporting of this study conforms to the STrengthening the Reporting of OBservational studies in Epidemiology Statement (STROBE).¹⁰

Participants. The study population consisted of all traceable Finnish patients with p.A1156T mutation-associated sodium channelopathy, in whom the diagnosis had been verified by molecular genetic methods through spring 2016 (n=29).⁷ One person was excluded due to cognitive impairment, one person was under 18 years old and 3 persons could not be contacted by mail. Hence, 24 persons were asked to participate in the survey.

Questionnaires. A questionnaire was developed for this survey. It contained the following validated items: 1) Pain intensity and interference subscales of the Brief Pain Inventory¹¹; 2) pain drawings (body maps) and Widespread Pain Index (WPI)¹² (range of scores 0 to 19); 3) the Finnish version of the RAND 36-item Short Form Health Survey (RAND-36)¹³; 4) the Finnish modification of the short form of the Beck Depression Inventory (RBDI)¹⁴.

Sociodemographic background, the occurrence of muscular pain, headache and gastrointestinal symptoms, non-painful muscular symptoms (unpleasant muscular sensations, weakness, stiffness, and difficulties in initiating or controlling movements), factors alleviating and exacerbating pain, and current pain medication were assessed. Designed for the purpose of this study, numerical rating scale (NRS) of 0–10 (0 = “no symptoms” 10 = “the worst possible intensity of the symptom”), multiple choice and open questions were used in the assessment. If applicable, an NRS score of 4 was chosen as the lower limit for moderate symptom intensity, because it is most commonly accepted for clinical use.¹⁵ We used similar approach in a previous survey of pain in myotonic

dystrophy type 2.¹⁶ Finnish language copies of this questionnaire are available from the author upon request. See supplementary materials for further details.

Statistical Analysis. Descriptive statistics, including medians and the first and third quartiles (i.e. interquartile range, IQR) were calculated using IBM SPSS Statistics for Macintosh, Version 24. We used one sample t-test for statistical comparison of mean QoL-values between the study sample and the general population. Because the population values were expressed as means, one sample t-test was used for this purpose, although RAND-36 subscales rarely conform to a normal distribution.¹⁷ The alpha-level was set at 0.05 for all tests. No adjustment was made for multiple testing.

Results

The response rate was 20/24 (83%). Table 1 shows demographic and clinical characteristics of the respondents. Pain was located over the limbs or trunk in 15/20 respondents (Figure). In 8/20 drawings, pain was bilaterally symmetric in all 21 defined areas. Median WPI was 8.5 (IQR 5-11.75), and $WPI \geq 7$ was reported by 14/ 20 responders. Pain intensity was highest in the areas of low back and lower limbs (median pain intensity for both was 6 on the NRS). Pain was increased by exercise in 78 % and cold in 50 % of patients, whereas pain was relieved by rest in 83 % and warmth in 61 %. Most respondents (16 / 20) reported multiple types of pain.

Unpleasant muscular sensations, muscle weakness, stiffness, and difficulties in initiating or controlling movements with intensity of NRS 4 or above were reported by 15 (75%), 13 (65%), 15 (75%), and 14 (70%) respondents, respectively. Headache occurring several days a week was reported by 6 / 20 respondents.

Pain medication, most commonly non-steroidal anti-inflammatory drugs (n = 12) and paracetamol (acetaminophen) (n = 8), was used on a weekly or daily basis by 14/ 20 (70 %) respondents. Other analgesics were

pregabalin (n = 2), codeine (n = 1), tramadol (n = 1), oxycodone (n = 1) and amitriptyline (n = 1). The assessed median efficacy of current pain medication was 6 (IQR 4-8) on the NRS.

Pain interference was highest in general activity (median 4.5, IQR 2-6.75 on the NRS) and normal work (median 4, IQR 3-7 on the NRS). Insomnia was reported by 8 responders. RAND-36 quality of life scores (Table 2) on the emotional and social domains were higher than the scores of physical domains.

Discussion

Exercise- and cold-induced, widespread pain was common in our cohort of patients. All respondents experienced pain during their course of illness. The severity and the impact of pain on daily life were variable. In this population, 27 % were incapacitated for work, compared to 6.4% of the Finnish general population.¹⁸ Pain interference was highest in the domains of general activity and normal work.

Half of the respondents reported pain less often than weekly. QoL subscales related to emotional well-being, emotional role functioning and social functioning were preserved, and severe depressive symptoms were rare. In this cohort of patients with a p.A1156T mutation, muscular symptoms dominated and other organ systems or mental health were much less affected. This is different than in myotonic dystrophy type 2 (DM2),¹⁶ in which pain was clearly associated with depressive symptoms and reduced emotional and social QoL. Also, in a previous cohort of patients with different *SCN4A* mutations (but not including p.A1156T) and DM2, QoL scores were higher in the *SCN4* mutation group than in the DM2 group.⁹

The exact mechanisms of pain in *SCN4A* mutation-associated channelopathies are not fully understood. Most *SCN4A* mutations cause gain-of-function defects, either disrupted inactivation or enhanced activation.⁴ Mildly attenuated fast inactivation by the p.A1156T channel, demonstrated by functional studies, does not cause clinical

myotonia or paramyotonia, although myotonic discharges had been detected by EMG in most such patients.⁷

Pain is reported in various proportions of myotonia patients with different *SCN4A* mutations.^{9,19,20}

Patients with certain muscular disorders, such as DM2 and myotonia congenita, can present with chronic widespread pain which may be indistinguishable from fibromyalgia.^{21,22,23} There is evidence that EMG abnormalities in patients with myalgia can differentiate an underlying channelopathy from non-specific myalgic syndromes.²⁴ In our patients with the p.A1156T mutation, initial EMG studies showed either myotonic discharges or increased insertional activity, as published previously.⁷

Diagnostic evaluations of non-myotonic dystrophies and many other genetic muscular syndromes can be challenging.⁹ The identification of a specific diagnosis underlying chronic widespread pain is important for avoiding wrong diagnoses, for precise nomenclature in daily practice and for future research on targeted pathophysiology and treatment. Multimodal and deconstructive strategies, such as the Research Domain Criteria (RDoC) framework, could help to integrate novel data on the research of the nature of complex phenomena including fibromyalgia and chronic pain.^{25,26}

There are several limitations in our study. The cross-sectional setting does not permit causal interpretations on the mechanisms of pain. The setting is also prone to recall bias. Both validated and customized instruments were used in this survey, which might have influenced the comparability of some of our results with previous research.

In conclusion, this channelopathy is another entity among the growing number of diseases causing widespread myalgic pain that resembles the pain of fibromyalgia syndrome.

List of acronyms/abbreviations

CLCN1 skeletal muscle voltage gated chloride channel gene

DM2 myotonic dystrophy type 2

IQR interquartile range

Nav voltage-gated sodium channel

NRS numerical rating scale

QoL quality of life

RAND-36 RAND 36-item Short Form Health Survey

RBDI Finnish modification of the short form of the Beck Depression Inventory

RDoC Research Domain Criteria

SCN4A skeletal muscle voltage gated sodium channel gene

WPI Widespread Pain Index

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Table 1. Demographic and clinical characteristics of the respondents

Respondent characteristics (n = 20)	
Age, median (range)	53 (20 – 79)
Gender, female, n (%)	13 (65)
Incapacitated for work, n (%) [*]	4 (27)
Current pain reported, n (%)	16 (80)
Pain previously but not currently, n (%)	4 (20)
Depression scores (as measured by RBDI[†])	
0 – 4 (no depression), n (%)	14 (70)
5-7 (mild depression), n (%)	5 (25)
8- 15 (moderate depression), n (%)	1 (5)
16- 39 (severe depression), n (%)	0 (0)
Pain intensity during the last week (NRS)[‡]	
At its worst, median (IQR [§])	6 (5-8.75)
On average, median (IQR [§])	5 (4-6.75)
At its least, median (IQR [§])	1 (0-3)
Occurrence of the most disturbing pain	
occasionally, n (%)	6 (30)
monthly, n (%)	4 (20)
weekly , n (%)	3 (15)
daily, n (%)	5 (25)
continuously, n (%)	2 (10)

^{*} Of working-age respondents (16–64 years, n = 15).

[†] RBDI: The Finnish modification of the short form of the Beck Depression Inventory.

[‡] Measured by the Brief Pain Inventory (BPI). Numeric rating scale (NRS) 0-10, where 0: “no pain” and 10: “worst possible pain”.

[§]IQR: interquartile range.

Table 2. Quality of Life RAND-36 scores and comparison to Finnish reference data*

Subscale	Study sample Median (IQR [†])	Study sample Mean (SD [‡])	General population [§] Mean (SD [‡])	p-value
Role functioning/emotional	100 (33.3-100)	68.4 (39.2)	75.0 (36.4)	0.47
Social functioning	87.5 (53.13-100)	76.4 (30.9)	82.1 (23.2)	0.24
Emotional well-being	80 (69-91)	76.4 (19.5)	73.7 (19.7)	0.54
Physical functioning	61.1 (45-80)	61.4 (26.0)	84.9 (20.1)	0.001
Energy	53.3 (35-76.67)	54.3 (20.9)	64.0 (22.4)	0.52
General health	50 (37.5-58.75)	48.5 (17.3)	65.0 (19.8)	<0.001
Bodily pain	45 (35-73.75)	50.6 (24.5)	76.2 (24.0)	<0.001
Role functioning/physical	25 (25-75)	36.3 (40.9)	74.8 (35.5)	<0.001

* Range 0-100, with higher scores indicating a better health state.

[†] IQR: interquartile range.

[‡] SD: standard deviation.

[§]Finnish general population values.¹³

Figure Legends:

Figure. Pain location and prevalence, data collected from pain drawings.

